REMARKS

Applicants wish to thank Examiner Naff for extending the courtesy of an interview to Applicants' representative, Nair Flores, on January 26, 2005. Examiner suggested that conditions be put in the claims that are considered to distinguish over the references, and establish that the condition are critical to the invention and not disclosed by the references. As discussed below, Applicant has addressed the Examiner's observations regarding new Claims 16-26 as well as amended Claims 13, 14, and 15.

Additionally, Claims 13, 14 and 15 have been amended to correct any grammatical errors and informalities. New Claims 16-26 are well supported in the specification and present no new matter. Finally, Applicants have canceled claims 1-12 without prejudice or disclaimer. Reconsideration of the rejections and objections set forth in the Office Action dated October 5, 2004 is respectfully requested.

Claim Rejections - 35 U.S.C. § 112, ¶ 1

The Examiner has rejected claims 1, 2 and 4-15 under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for fibroin as required by claim 3, does not reasonably provide enablement for any other fibroin. While the claims in question have been canceled without prejudice, Applicants have added new claims directed to the same subject matter.

Applicants disagree with the Examiner's characterization regarding lack of enablement for other fibroin. Section 2164.02 of the MPEP clearly states that "[t]he presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure." Furthermore, the specification recites, "natural fibroin – e.g. obtained from, but not exclusively from the *Bombyx mori* silkworm" (Page 15, Line 27-30). In addition, fibroin produced by different silkworms, for example, is the same regarding its chemical properties. In other words, there are no appreciable differences in their chemical properties, e.g. sericins can be removed from silk obtained from different silkworms in the same way, fibroin water solutions can be prepared in the same way, fibroin films can cast from the fibroin-water

solution, etc. Accordingly, Applicants submit that other types of natural fibroin are well supported in the specification.

Claim Rejections - 35 U.S.C. § 112, ¶ 2

The Examiner has rejected claims 1-15 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants have canceled claims 1-12 without prejudice. In addition, Applicants have amended claims 13, 14 and 15. Claims 13 and 14 set forth clear process steps for a complete process of using the bio-membrane to form tissue. Claim 15 sets forth clear and distinct and positive process steps.

Claim Rejections - 35 U.S.C. § 102

The Examiner has rejected claims 1-15 under 35 U.S.C. § 102 as being anticipated by Santin et al or Gotoh et al. Applicants have cancelled claims 1-12 and have amended claims 13, 14 and 15. Applicants disagree with Examiner that Claims 13, 14 and 15 are anticipated by Santin or Gotoh.

In particular, neither Santin nor Gotoh teach the potential use of beta-form fibroin films for tissue engineering. Claims 13 and 14 are directed to the use of a bio-membrane containing fibroin to seed human tissue cells. Santin evaluates the inflammatory potential of silk fibroin films by measuring the amount of fibrinogen that binds to fibroin films, after contact with human plasma, in comparison with other reference materials. Santin, however, does not assess or teach the ability of fibroin to promote cell adhesion, proliferation or differentiation as in the present Application. Gotoh, on the other hand, teaches silk fibroin to coat polystyrene cell culture dish walls. While polystyrene containers may be used in the present application, any other type of support can be used. What is more, Gotoh does not teach using silk fibroin films as substrates for tissue engineering applications, but only as a coating for cell culture dishes made of polystyrene. Thus, Applicants submit that claims 13 and 14 are not anticipated by Santin or Gotoh, and therefore, the rejection to claims 13 and 14 should be withdrawn.

Likewise, Santin and Gotoh fail to teach a method of the production of a substrate as described in Claim 15. In particular, neither Santin or Gotoh teach the utilization of a membrane with a 3500 molecular weight cut-off for dialysis. Thus Applicants submit that Claim 15 is not anticipated by Santin or Gotoh, and therefore, the rejection to Claim 15 should be withdrawn.

Claim Rejections - 35 U.S.C. § 103

The Examiner has rejected claims 1-15 under 35 U.S.C. 103(a) as being unpatentable over Capello U.S. Patent 5,606,019 or Tsubouchi U.S. Patent 6,440,740 (Tsubouchi '740), or Tsubouchi U.S. Patent 6,174,053 (Tsubouchi '053) in view of Santin and Gotoh. Applicants have cancelled claims 1-12 and have amended claims 13, 14 and 15. Claims 13, 14 and 15 are not unpatentable over Cappello or Tsubouchi '740 or Tsubouchi '053.

The Examiner has not met his burden to prove a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, one of the basic criteria that must be met is that the prior art reference must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Claims 13 and 14 are directed to the use of a bio-membrane containing fibroin to seed human tissue cells. Capello does not teach the use of fibroin in bio-membranes, but rather the use of aminoacids in fibroin. Capello teaches the synthesis of copolymers of aminoacids, some of them being present in fibroin, and elastine. Capello does not teach the use of the fibroin molecule as a whole but aminoacid sequences present various copolymers such as fibroin. The bioactive behavior of the fibroin molecule is much higher than the bioactivity of the aminoacid sequence. Therefore, Capello in fact teaches away from using the fibroin molecule because Capello requires a different bioactivity than that of this invention. In addition, Cappello disclose the use of beta-from fibroin.

Furthermore, Tsubouchi '740 or Tsubouchi '053 do not teach crystalline beta-form fibroin. Tsubouchi '053 teaches fibroin used in an non-crystalline form, i.e. with a degree of crystallization that remains below 10%, or in a powder form. The addition of sericin modifies

the structure and properties of fibroin. As such, Tsubouchi '053 teaches away from using beta-form fibroin in crystalline form as it is used in the present disclosure.

Thus Applicants submit that Claims 13 and 14 are not rendered obvious by Capello or Tsubouchi '740 or Tsubouchi '053 in view of Santin and Gotoh, and therefore, request that the rejection to Claims 13 and 14 be withdrawn.

Claim 15 is directed to a method of the production of a substrate using fibroin. Neither Capello or Tsubouchi '740 or Tsubouchi '053 teach a method for the production of a substrate utilizing a membrane with a 3500 molecular weight cut-off for dialysis. As aforementioned, Santin and Gotoh do not teach using a dialysis membrane with a molecular weight cut-off of 3500. Thus Applicants submit that Claim 15 is not rendered obvious by Capello or Tsubouchi '740 or Tsubouchi '053 in view of Santin and Gotoh, and therefore, request that the rejection to Claim 15 be withdrawn.

Support for Amended Claims

Claims 13-15 are well supported in the specification. In particular:

Claim 13 is at least supported by the following specification cites. Crystalline fibroin is supported in page 24, lines 17-19. Beta-form fibroin is supported in page 25, line 12 and page 27, line 8. Seeding human tissue cells on a bio-membrane is supported in page 16, line 4. Permitting human tissue cells to proliferate and differentiate is supported in page 18, line 23-25. Forming tissue on the bio-membrane is supported in page 19, lines 3-5.

Claim 14 is at least supported in page 16, lines 12-22 where the use of multiple types of human cells is described.

Claim 15 is at least supported in page 26, lines 20-30 and page 27, lines 1-6 where the preparation of the fibroin membrane is described.

New Claims

Applicants have added claims 16-26 which do not present new matter. Claims 16-25 depend from claim 13. As discussed above, claim 13 is not anticipated by Santin nor Gotoh. Additionally, Claim 13 is not rendered obvious by Tsubouchi '740 or Tsubouchi '053 or Capello in view of Santin and Gotoh. Finally claim 13 is well supported in the specification. Applicants have also added new independent claim 26 which is not anticipated by Santin nor Gotoh and is not obvious in view of Tsubouchi '740 or Tsubouchi '053 or Capello in view of Santin and Gotoh for the same reasons Claim 15 is not anticipated or rendered obvious by said references.

Support for New Claims

Claims 16-26 are well supported in the specification. In particular:

Claims 16 and 17 are at least supported in page 16, line 27 and page 17, line 21 where cells from one or more individuals are used.

Claim 18 is at least supported in page 17, lines 9-14 where consumption of glucose by the human tissue cells is recorded, and the human tissue cells secrete lactic acid.

Claim 19 is at least supported in page 18, lines 21-23, where the use of human fibroblasts is described in conjunction with allowing the fibroblasts to secrete extracellular matrix components and precursors to collagen fibers.

Claim 20 is at least supported in page 19, lines 14-26, where the use of human keratinocytes to form epithelium is described.

Claim 21 is at least supported in page 21, lines 7-9, where it is disclosed that the simultaneous presence on the fibroin bio-membrane of pre-irradiated human fibroblasts is capable of significantly stimulating the proliferative activity of the human keratinocytes and thereby preventing the onset of the diffpoptosis phenomenon.

Claim 22 is at least supported in page 15, line 30 where fibroin secreted by the *Bombyx mori silkworm* is disclosed.

Claims 23 and 24 are at least supported in page 15, line 16 and page 15, line 30 where use of polymers of natural and synthetic origin is disclosed.

Claim 25 is at least supported by Claim 10 of the original as filed application.

Claim 26 is at least supported in page 26, lines 20-30 and page 27, 1-6 where the preparation of the fibroin membrane is described.

Accordingly, Claims 16-26 are allowable for at least the foregoing reasons.

Conclusion

Claims 1-12 have been canceled without prejudice or disclaimer. As such, Applicants reserve the right to continue prosecution of similar claims in future applications. As for the new and currently amended claims, Applicants submit that the claims are in condition for allowance.

The Director is authorized to charge any additional fee(s) or any underpayment of fee(s), or to credit any overpayments to Deposit Account Number 50-2638, Deposit Account Name Greenberg Traurig, LLP. Please ensure that the Attorney Docket Number is referred to when charging any payments or credits for this case.

Respectfully submitted,

GREENBERG TRAURIG, LLP

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By Pablo Tapia
Pablo E. Tapia
Registration No. 52,275

Greenberg Traurig, LLP
2450 Colorado Avenue, Suite 400
Santa Monica, California 90404
Telephone: 310-586-7700
Facsimile: 310-586-7800